COURS ST-PAUL

Cancer du col
Cas clinique : en rechute quelles options ?

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Liens d’intérêt

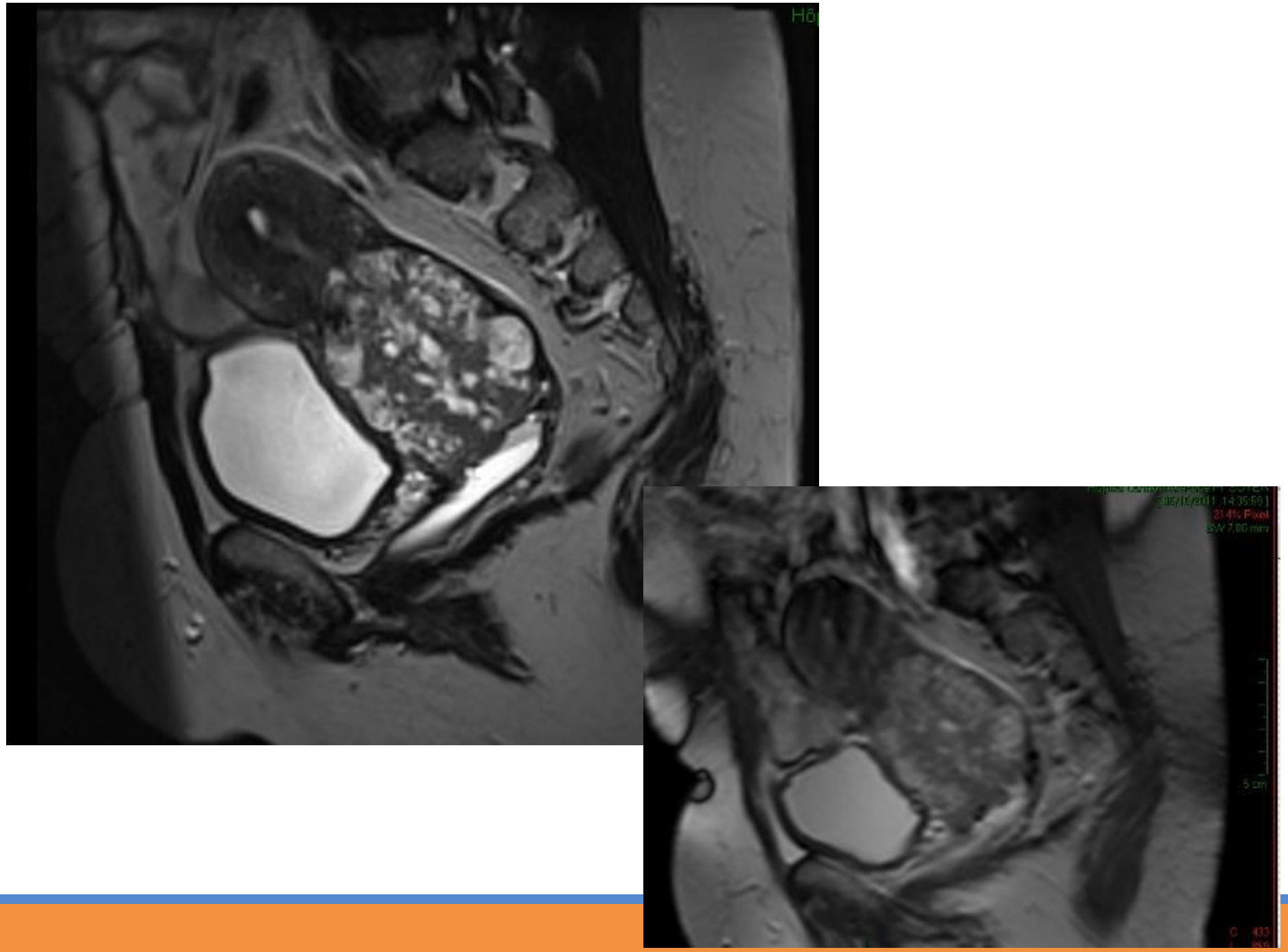
- - Astrazeneca , GSK, Sanofi, Roche , GSK Tesaro ,Seagen , Leo (consultancy and travel expenses)
- - Astrazeneca , GSK, Seagen , MSD, PharmaMar (consultancy and travel expenses)

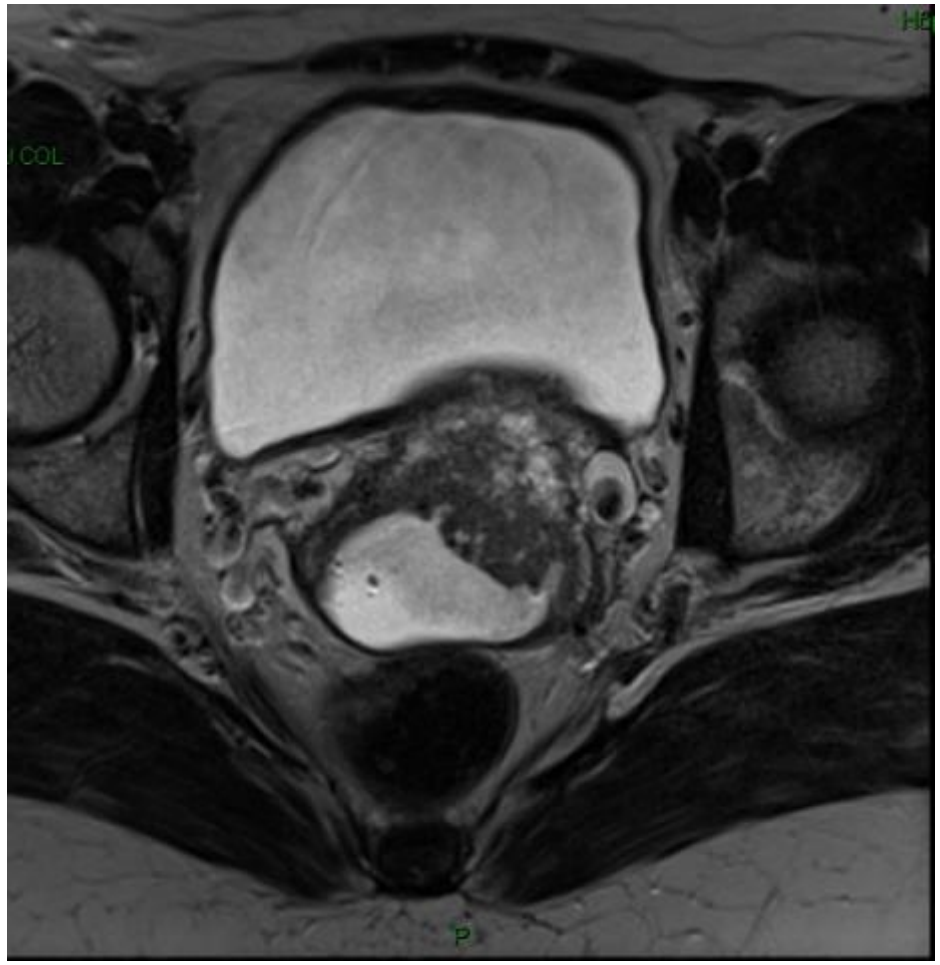
Cas clinique

- ✓Janvier 2021 Mme B. 36 ans; ATCD médico chir = 0
- ✓PR 13 ans; cycles réguliers. CO 8 ans
- ✓P1G5 1 accouchement normal d'une fille (14 ans); 1 FCS; 1 IVG. Pas de suivi gynécologique
- ✓Tabac = 20 paquets-année
- ✓Métrorragies depuis plusieurs mois, puis hémorragie d'origine gynéco : consultation en urgence
- Découverte d'une tumeur cervicale
  - Biopsie : carcinome épidermoïde peu différencié, invasif du col utérin
- Scanner abdo-pelv : doute sur une adénopathie iliaque interne droite de 15 mm de diamètre

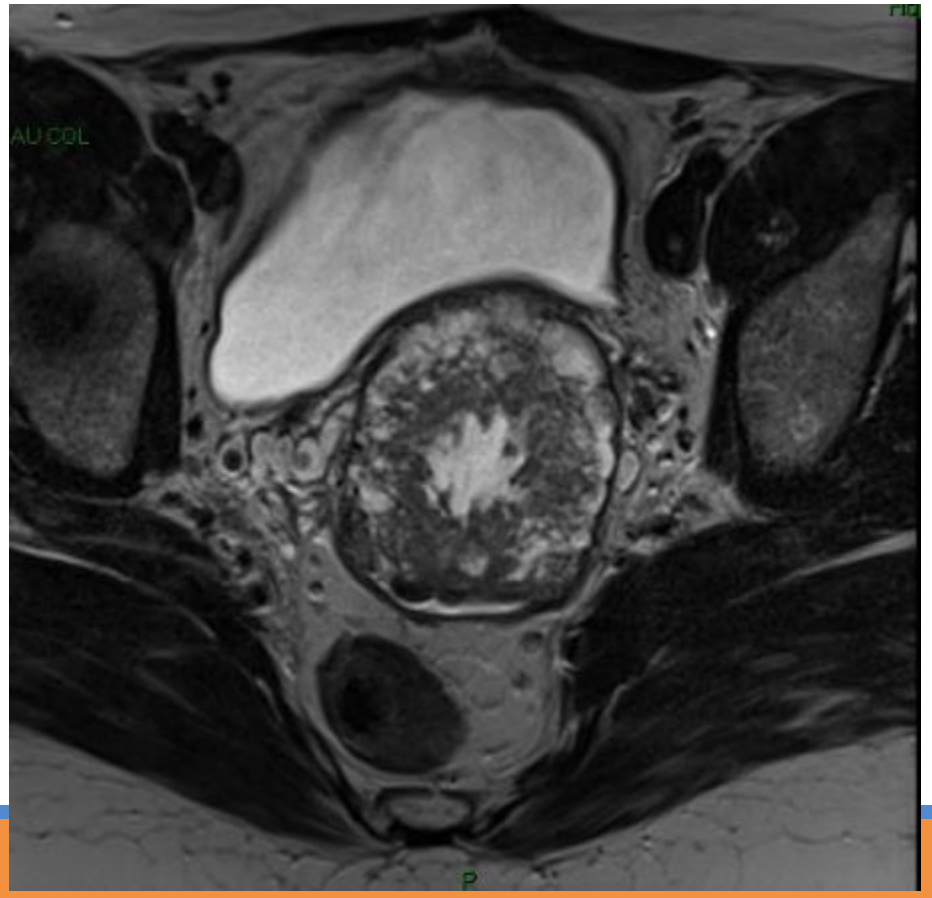
Cas Clinique

- Examen clinique :
  - La tumeur est à développement essentiellement postérieur, mesurant environ 6 cm de diamètre.
  - Atteinte du cul de sac vaginal postérieur.
  - Au TR : infiltration paramétriale proximale bilatérale prédominant à gauche
  - Pas d'adénopathie inguinale ni sus claviculaire.
  - Réalisation d’une IRM





FIGO 2013: IIB N+
FIGO 2018: IIIC1
TNM: T2BN1M0



Cas Clinique

- Pet-scanner négatif en LA; un curage lombo-aortique per coelio est négatif
- Traitement : Radiothérapie –chimiothérapie concomitante

  (RT externe + curie UV): février 2021- avril 2021; cisplatine 40 mg/ m^2/sem 5 sem
- Rémission complète à 6 semaines de la fin des traitements
- 15 mois + tard nov 2022 Mme B se présente à la consultation de surveillance
  - Radio de thorax : nodules bilatéraux
  - Biopsie : métastases d'un carcinome peu différencié d'origine cervicale
  - Pas de récidive pelvienne

Que proposez-vous?

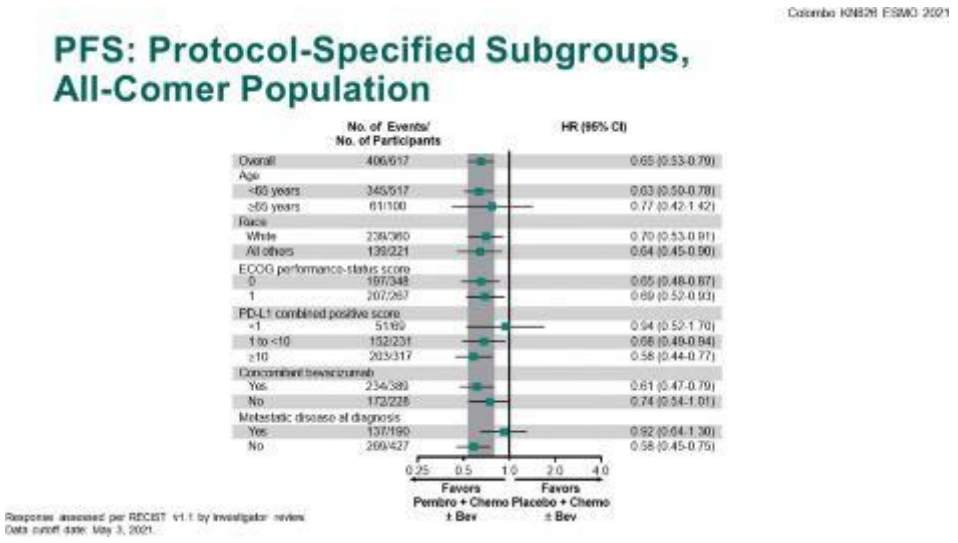
1. Cisplatine 50 mg/m²+ 5 FU 1g/m²/j 4j J1=J28
2. Cisplatine 50 mg/m² J1 + Taxol 135 mg/ m² 24h
3. Cisplatine 50 mg/m² J1 + Taxol 135 mg/ m² 24h + bevacizumab
4. Cisplatine 50 mg/m² J1 + Taxol 135 mg/ m² 24h + pembrolizumab
5. Carboplatine AUC 5 J1 + Taxol 175 mg/ m² 24h + pembrolizumab
6. Carboplatine AUC 5 J1 + Taxol 175 mg/ m² 3h + bevacizumab +pembrolizumab

Réponse 3,4,5,6 : en fonction du CPS

- 3 : si PD-L1 CPS < 1 : pas d'indication au pembrolizumab : GOG 240[1]
- 4-5: si PD-L1 CPS > 1 et CI au bevacizumab : keynote 826[2];

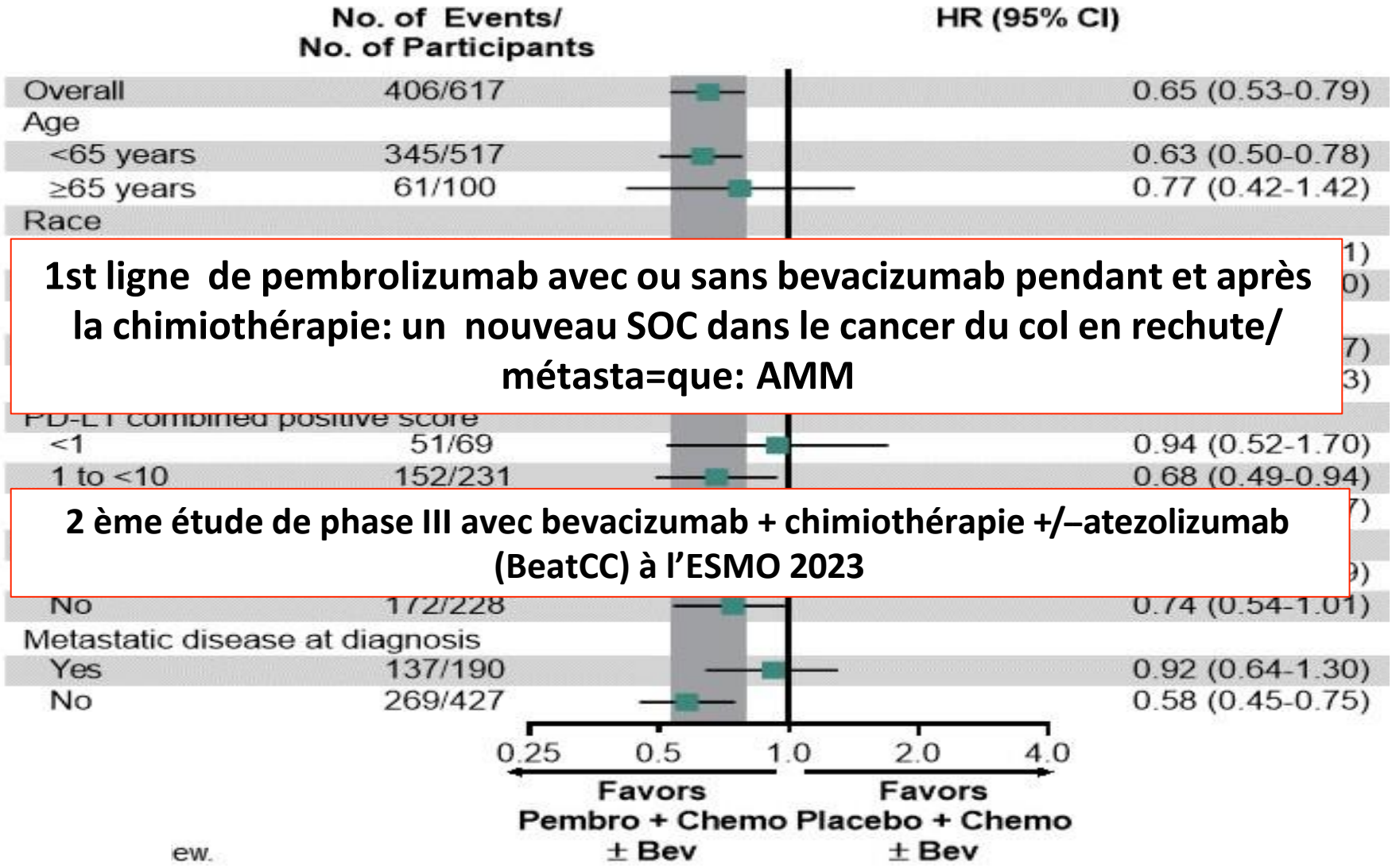
a déjà reçu du platine cisplatine ou carboplatine (décision fonction tox résiduelles ou potentielles)[3]

- 6: si PD-L1 CPS > 1 et absence de CI au bevacizumab : keynote 826



1: Tewari KS, *NEJM* 2014, *Lancet* 2017; 2 : Colombo N *NEJM* 2021; 3: Kitagawa R, *J Clin Oncol* 2015

Keynote 826: le pembrolizumab associé à la chimiothérapie augmente la PFS et l' OS dans le cancer du col métastatique en 1ère ligne; CPS>1



1st ligne de pembrolizumab avec ou sans bevacizumab pendant et après la chimiothérapie: un nouveau SOC dans le cancer du col en rechute/ métasta=que: AMM

2 ème étude de phase III avec bevacizumab + chimiothérapie +/–atezolizumab (BeatCC) à l'ESMO 2023

Colombo et al ESMO 2021 and NEJM Sept 2021, Oaknin A ESMO 2023

Confirma=on bénéfice de l'immunothérapie en 1ère ligne méta

essai BeatCC
Oaknin A, ESMO virtual PS Nov 23

BEATcc trial design (NCT03556839)

Open-label, multicentre, randomised, phase 3 trial in an all-comer population

- Metastatic, persistent or recurrent cervical cancer not amenable to curative therapy
- GOG/ECOG PS ≤1
- No prior systemic anti-cancer therapy for R/M CC
- In patients with pelvic disease, no bladder or rectal mucosa involvement
- Available archival or fresh tumour sample for PD-L1 expression

R 1:1 N=410

- Atezolizumab 1200 mg + bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w
- Bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

Continued until disease progression/unacceptable toxicity
Patients with CR after ≥6 cycles could stop chemotherapy and continue biological therapy alone
Crossover from standard arm at progression not permitted

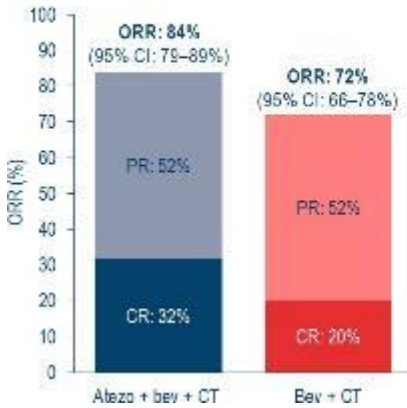
Dual primary endpoints
- Investigator-assessed PFS (RECIST 1.1)
- OS

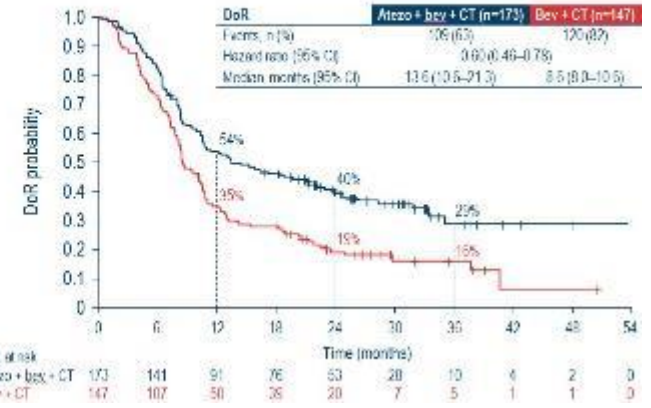
Key secondary endpoints
- ORR (RECIST v1.1)
- DoR (RECIST v1.1)
- TFST
- PFS2
- Safety

Stratification factors:
- Prior concurrent chemoradiation (yes vs no)
- Histology (squamous cell carcinoma vs adenocarcinoma[b] including adenosquamous carcinoma)
- Chemotherapy backbone (cisplatin vs carboplatin)

[a]Paclitaxel 175 mg/m² day 1 + platinum (cisplatin 50 mg/m² or carboplatin AUC5) day 1; [b]Capped at 20% of the overall population
CR = complete response; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; PFS2 = time from randomisation to second progression or death; PS = performance status; q3w = every 3 weeks; TFST = time from randomisation to first subsequent therapy or death

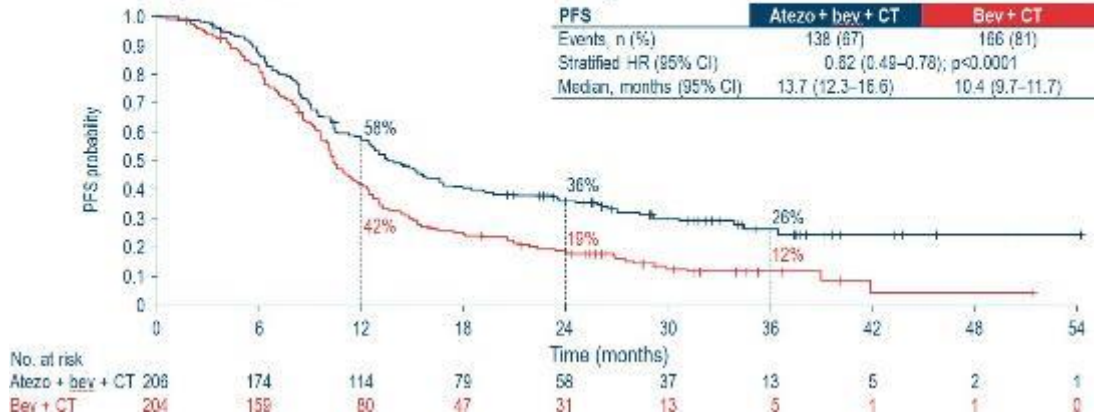
Secondary endpoints: ORR and DoR





Dual primary endpoint: PFS

Statistically significant 38% reduction in risk of progression or death



Dual primary endpoint: OS (interim analysis)

Statistically significant 32% reduction in risk of death

Question

Même question avec récidive pelvienne associée

Même réponse mais pour 3 et 6 : discuter de l’introduction du bevacizumab en RCP : risque fistulaire+++

1 ère ligne de traitement 2023: CT+ Bev +/–IO

RPC 2023

Traitement de première ligne
Tumeur exprimant PD-L1 (CPS ≥1)

- Dans tous les cas: il est recommandé d'inclure les soins de support dans la prise en charge initiale et de favoriser les inclusions dans les essais cliniques
- **Standard:**
  - Sel de platine* (carboplatine AUC 5 ou cisplatine 50 mg/m²) + paclitaxel 175mg/m² /3 h + pembrolizumab 200 mg +/- bevacizumab 15mg/kg J1 q21 pour 6 cycles
  - suivi de: pembrolizumab 200 mg (au moins 2 cycles si RC, max 35 cycles) +/- bevacizumab 15mg/kg J1 q21 (jusqu'à toxicité ou progression)

Niveau 1 Grade A

RPC 2023

Traitement de première ligne
Tumeur n'exprimant pas PD-L1 (CPS < 1)

- Dans tous les cas: il est recommandé d'inclure les soins de support dans la prise en charge initiale et de favoriser les inclusions dans les essais cliniques
- **Standard:**
  - Sel de platine* + paclitaxel 175mg/m² /3 h + bevacizumab J1 q21
  - Jusqu'à progression
  - À ajuster selon la toxicité

Niveau 1 Grade A

- **Options:**
  - cisplatine 50mg/m² J1 + paclitaxel 135mg/m² /24h J1 q21
  - cisplatine 50mg/m² J1 + topotécan 0,75mg/m²/j J1-3 q21
  - paclitaxel 175mg/m² /3h J1 + topotécan 0,75mg/m²/j J1-3 q21 +/- bevacizumab

Patiente traitée en nov 2021 de la récidive métastatique

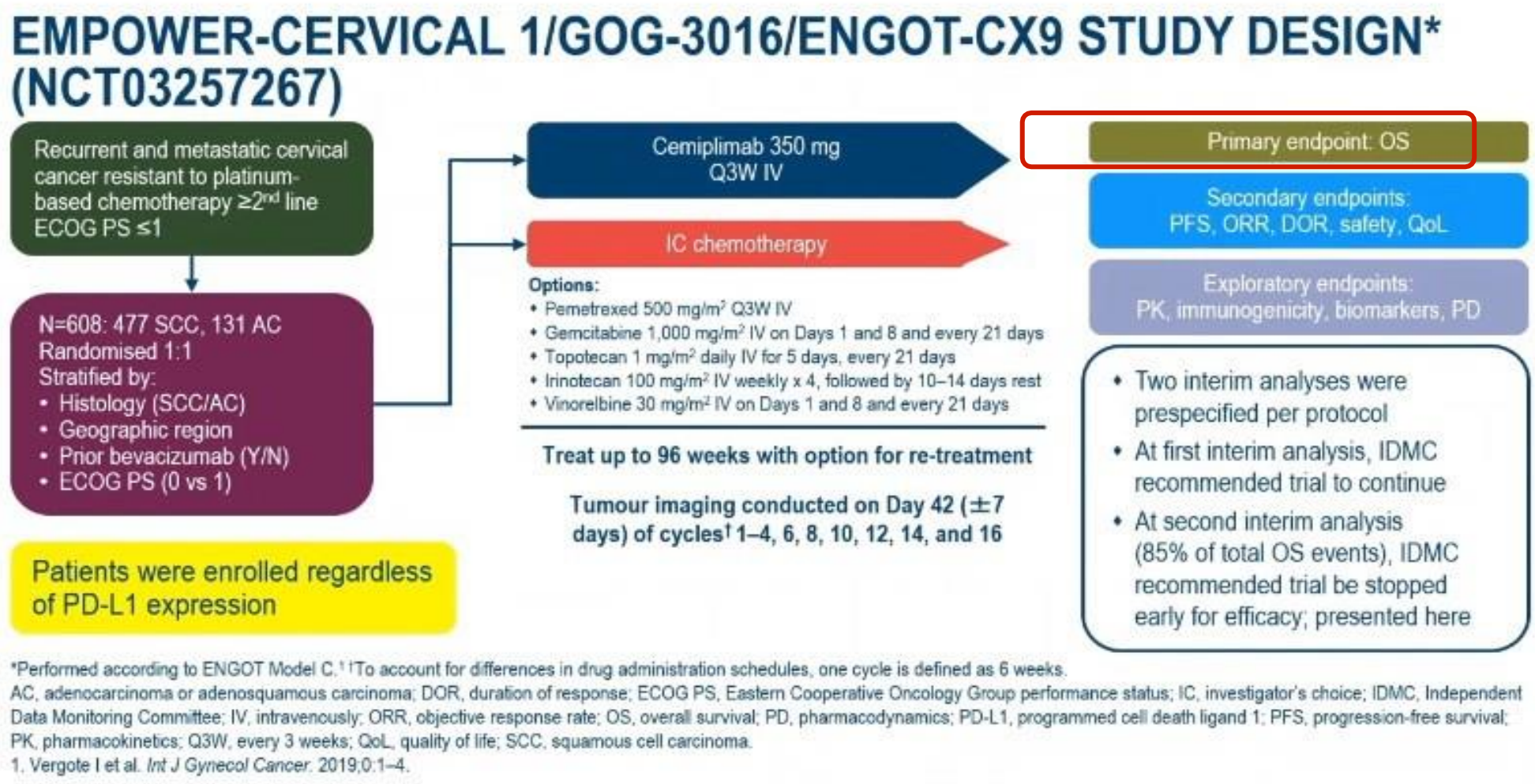
- A reçu carboplatine paclitaxel bevacizumab pendant 18 mois
- Reprise évolutive multiple en décembre 2023
- Impossible de faire le CPS sur petite biopsie initiale
- Que proposez-vous?
    1. Reprise d'une chimiothérapie carboplatine taxol en fonction de la toxicité
    2. Cemiplimab 350 mg IV tous les 3 semaines après biopsie pour CPS et si CPS >1
    3. Cemiplimab 350 mg IV tous les 3 semaines

Réponse 1 et 3

- Intervalle libre sans platine peut justifier de reprendre le platine qui a été efficace
- N’a pas reçu d’immunothérapie
- Cemiplimab > chimiothérapie de seconde ligne (monochimio sans platine) quel que soit le statut PD-L1
- AMM et remboursement déc 23

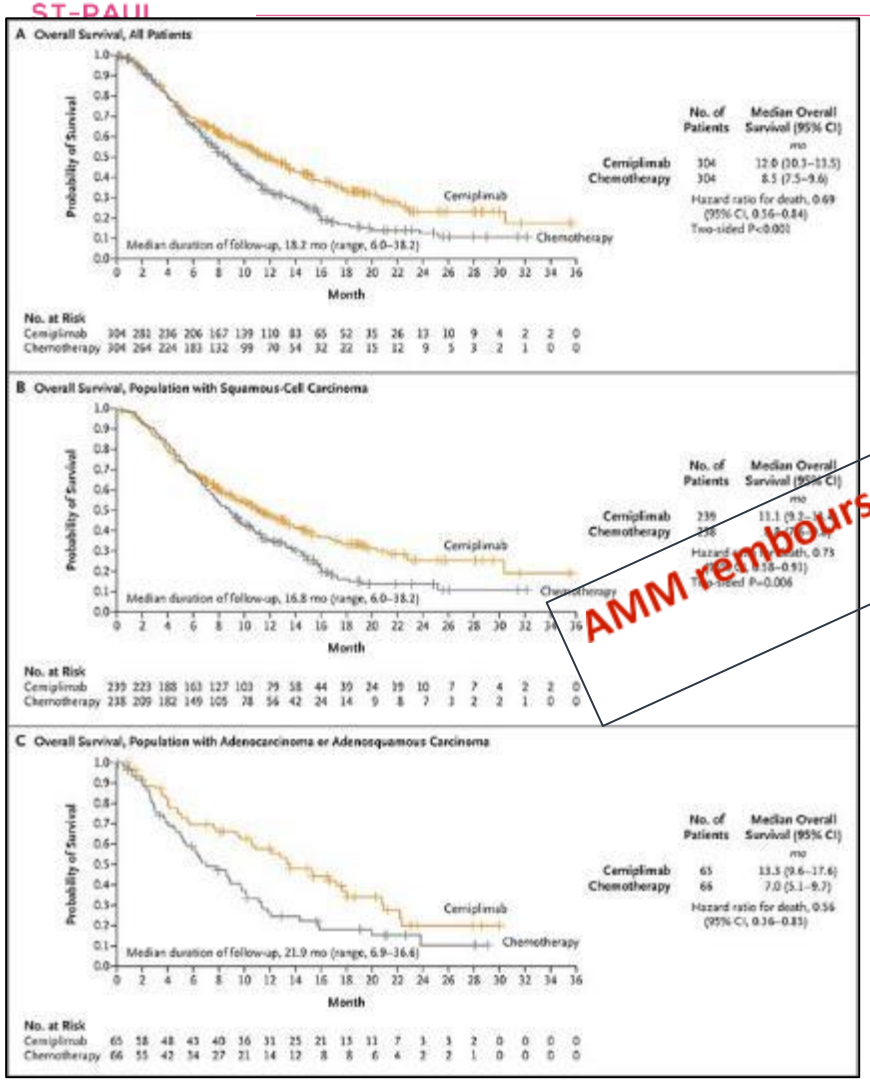
Phase III Anti PD1 (cemiplimab) *vs* chimio en récidive: EMPOWER

R au pla:ne
≥ 2 lignes
Prétraitées par
- Taxol
- Bevacizumab

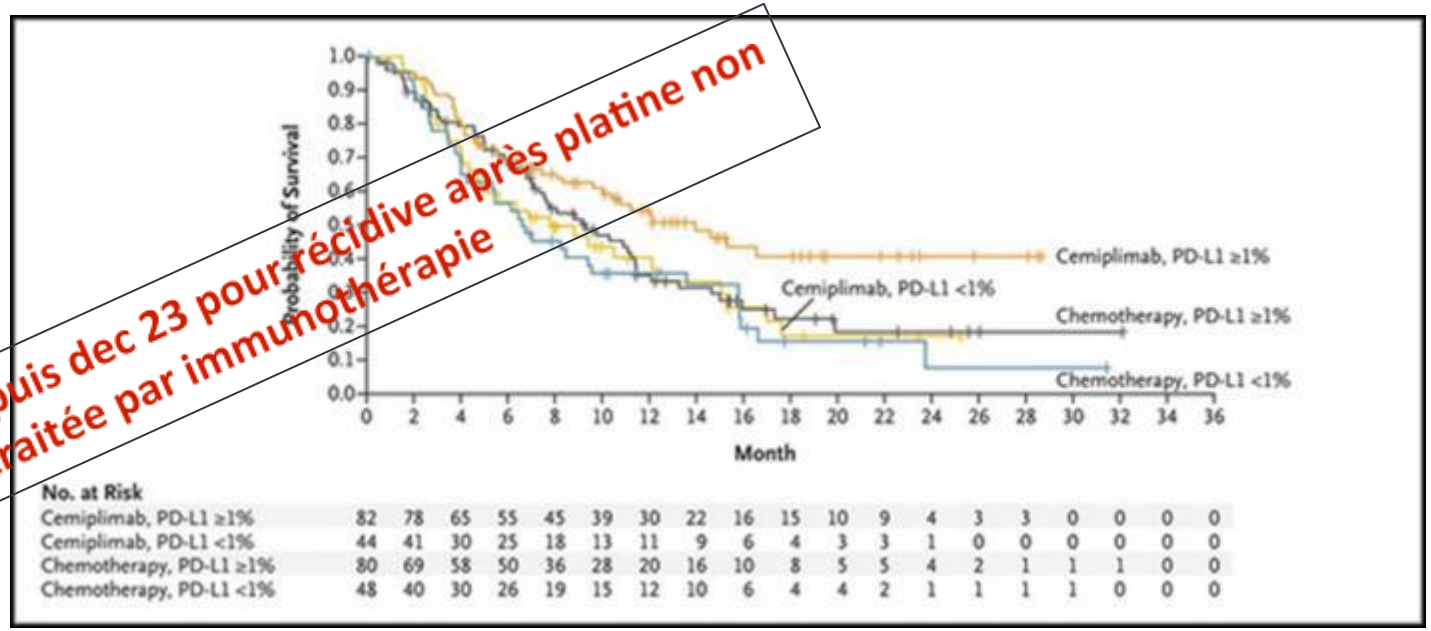


Tewari WS NEJM 2022; 386:544--555,

Survie globale en fonction de l'histologie et du statut PD-L1

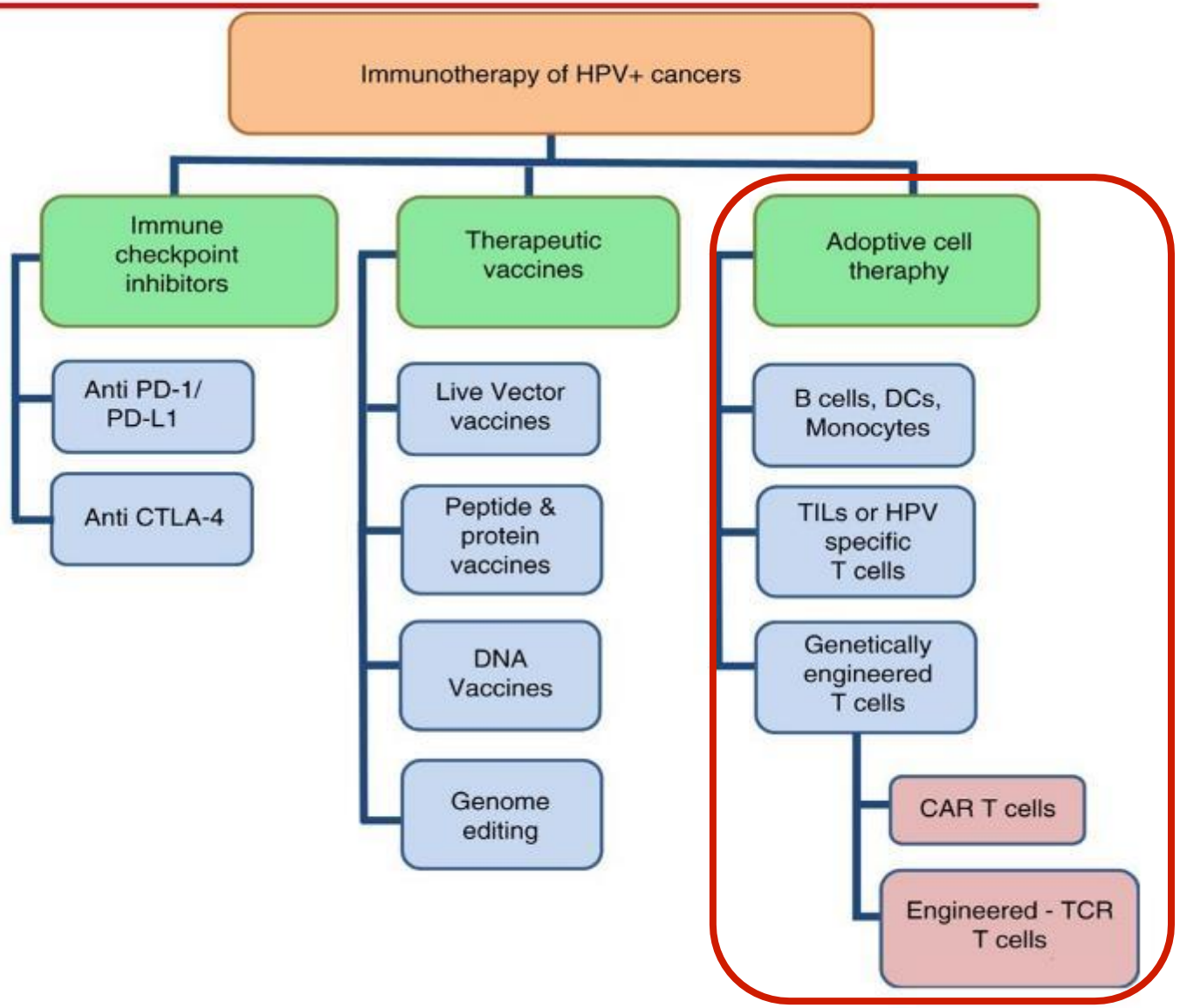


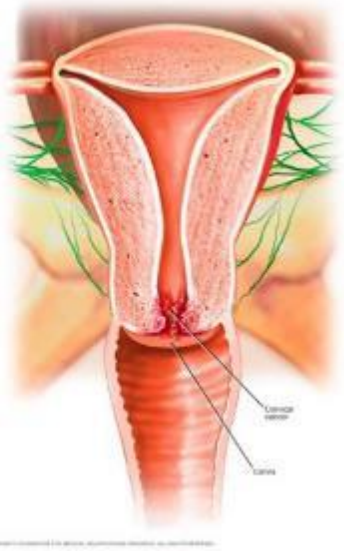
AMM remboursée depuis dec 23 pour récidive après platine non pré traitée par immunothérapie



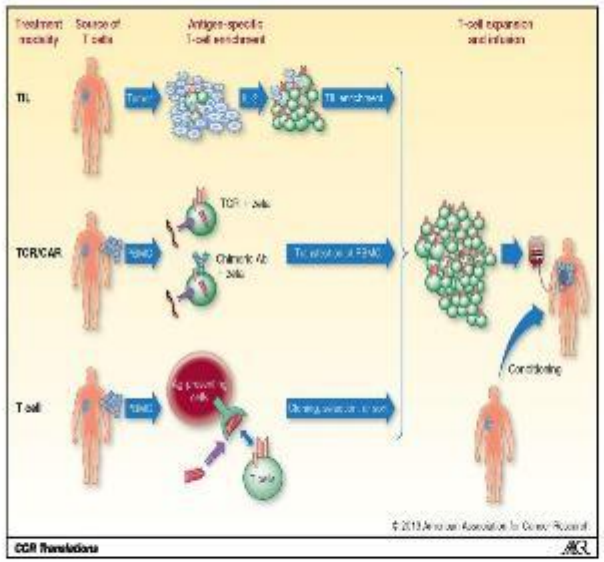
Tewari WS, *N Eng J Med* 2022; 386:544–555

Immunotherapy in Cervical Cancer



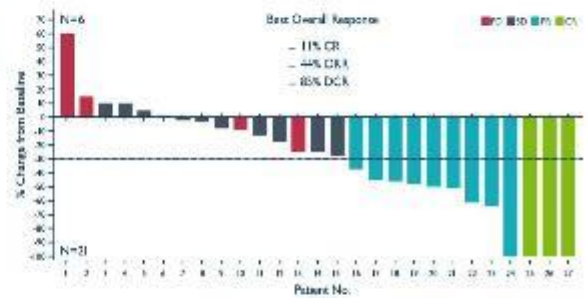


Adoptive T cell therapies



Yee C. Clin. Can. Res. 2013

Adoptive T cell therapies: TIL therapy



At median follow up of 7.4 months the median DOR has not been reached:
– range 2.6+ to 9.2+ months

Jazaeri et al., ASCO 2019

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Patiente traitée en nov 2021 de la récidive métastatique

- A reçu carboplatine paclitaxel bevacizumab pendant 12 mois
- Reprise évolutive multiple en décembre 2023
- Cemiplimab 350 mg IV tous les 3 semaines pendant 5 mois
- Progression multiple que proposez vous ?

Phase 3 innovaTV 301 : A Randomized, Open-Label, Phase 3 Trial

Key Eligibility Criteria

- Recurrent or metastatic cervical cancer
- Disease progression on or after chemotherapy doublet ± bevacizumab and an anti-PD-(L)1 agent, if eligible and available
- ≤2 prior lines
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

Randomization 1:1

N=502

Stratified by:

- **ECOG PS (0 vs 1)**
- **Prior bevacizumab (yes vs no)**
- **Prior anti-PD-(L)1 therapy (yes vs no)**
- **Geographic region (US, Europe, Other)**

Treatment

Tisotumab Vedotin (n=253)

2.0 mg/kg IV Q3W

IC Chemotherapy[a] (n=249)

- Topotecan
- Vinorelbine
- Gemcitabine
- Irinotecan
- Pemetrexed

Outcomes/Endpoints

Primary Endpoint

- OS[b]

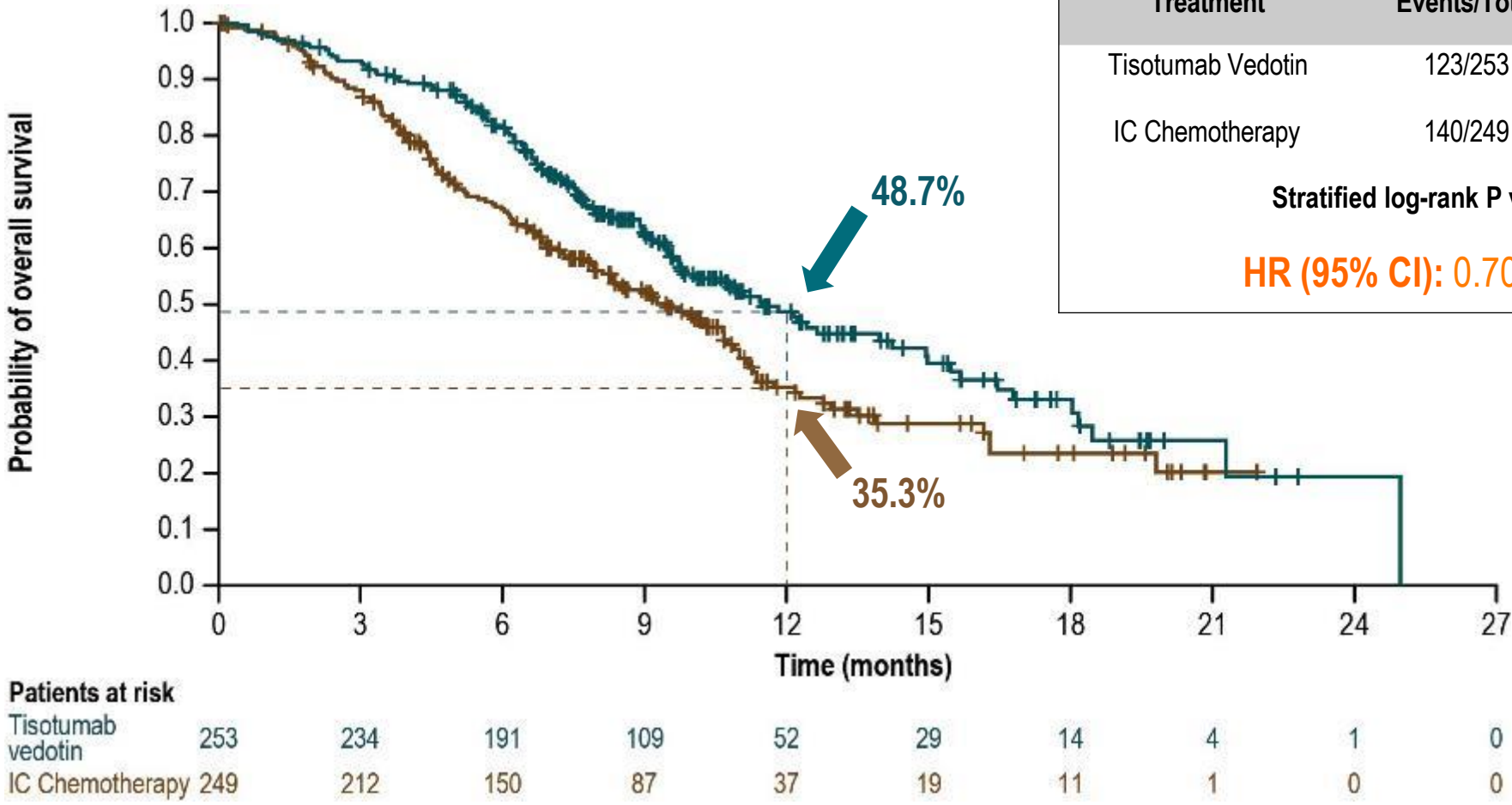
Key Secondary Endpoints

- PFS[c]
- ORR[c]
- Safety

- IC, investigator's choice
- End of treatment visit occurred 30 days after the last dose of treatment. Survival follow-up occurred every 60 days after the last dose of treatment.
- [a]Chemotherapy regimens were given at the following doses: topotecan: 1 or 1.25 mg/m^2 IV on Days 1 to 5, every 21 days; vinorelbine: 30 mg/m^2 IV on Days 1 and 8, every 21 days; gemcitabine: 1000 mg/m^2 IV on Days 1 and 8, every 21 days; irinotecan: 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days; pemetrexed: 500 mg/m^2 on Day 1, every 21 days; [b]OS was defined as the time from the date of randomization to the date of death due to any cause; [c]Assessed by investigator

Phase 3 innovaTV 301 : A Randomized, Open-Label, Phase 3 Trial

OS



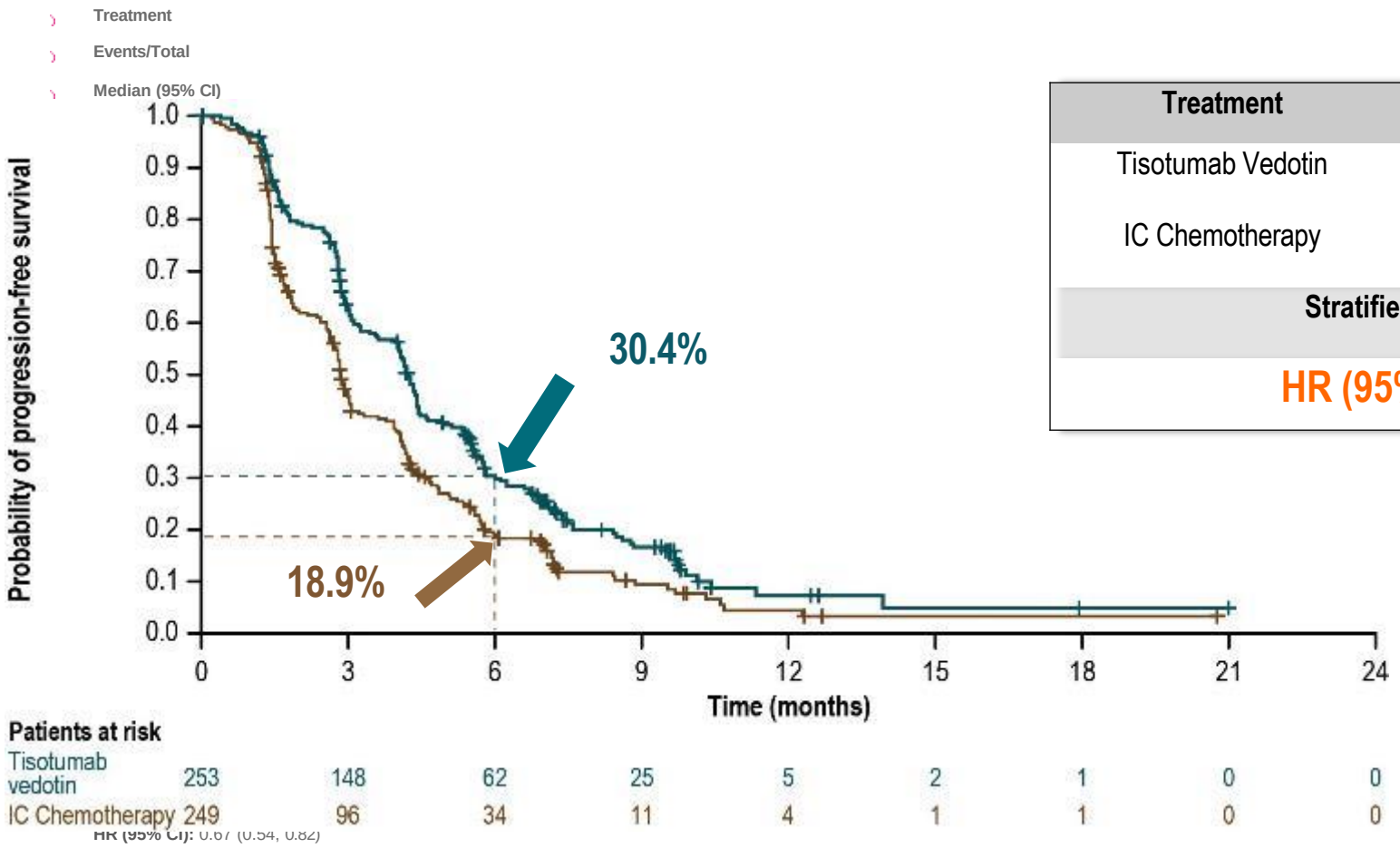
Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	**11.5 (9.8, 14.9)**
IC Chemotherapy	140/249	**9.5 (7.9, 10.7)**

Stratified log-rank P value[a]: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)

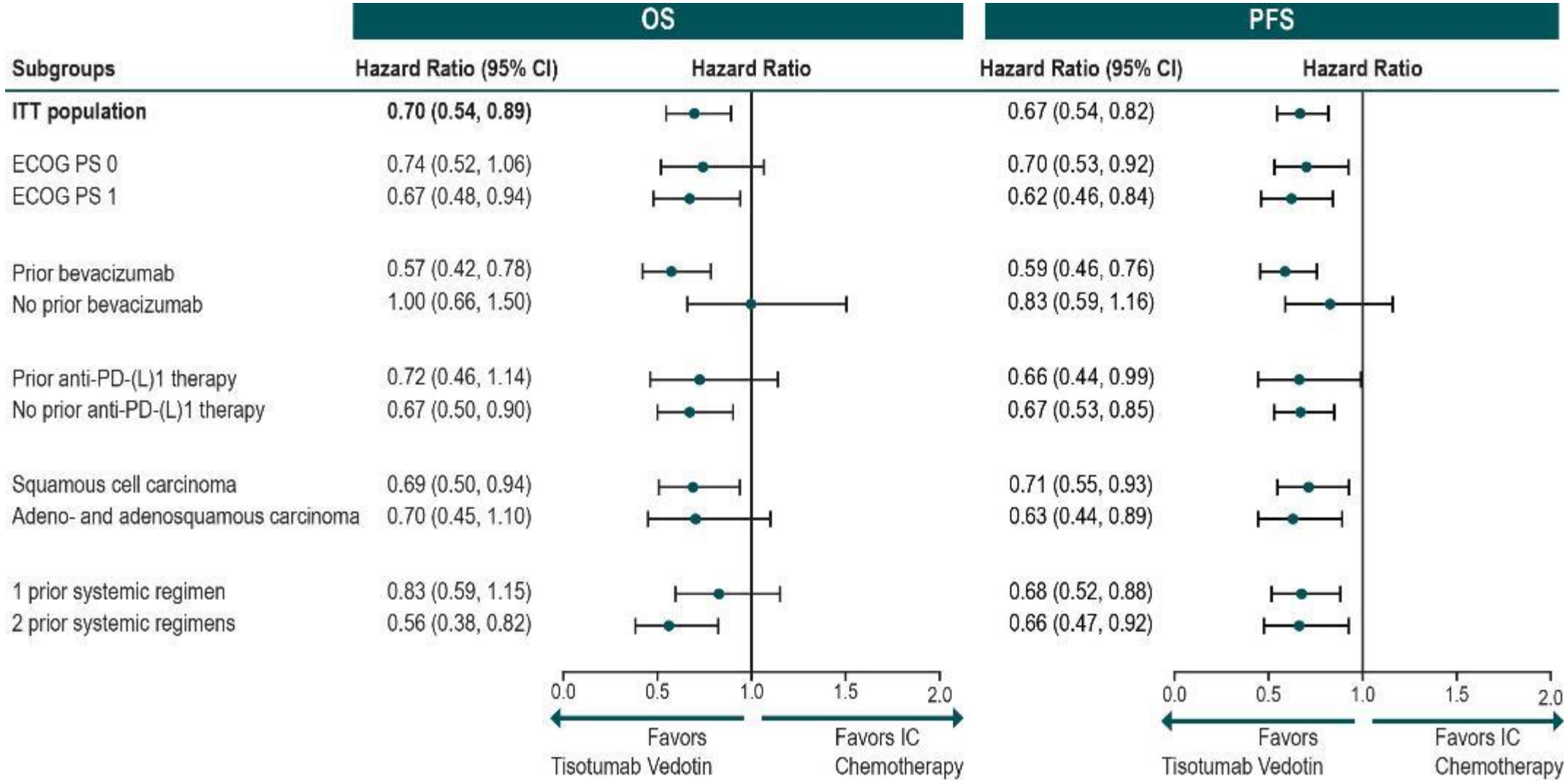
Phase 3 innovaTV 301 : A Randomized, Open-Label, Phase 3 Trial

PFS



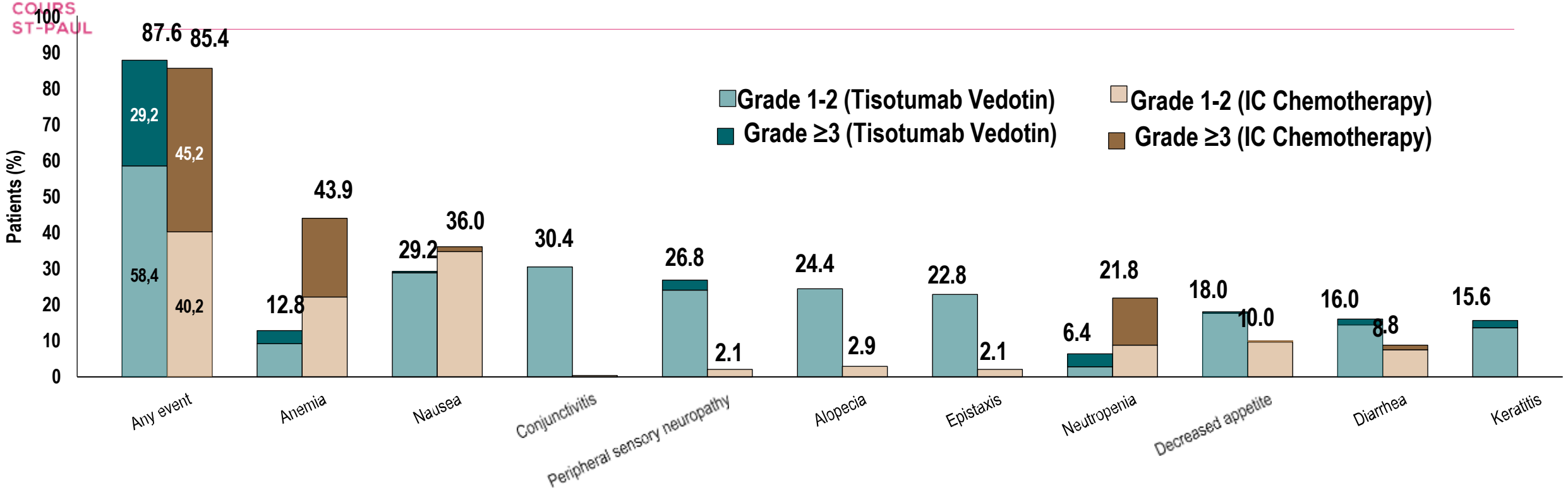
Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	198/253	**4.2 (4.0, 4.4)**
IC Chemotherapy	194/249	**2.9 (2.6, 3.1)**
Stratified log-rank P value[a]: <0.0001		
HR (95% CI): 0.67 (0.54, 0.82)		

Phase 3 innovaTV 301 : A Randomized, Open-Label, Phase 3 Trial



Phase 3 innovaTV 301 : A Randomized, Open-Label, Phase 3 Trial

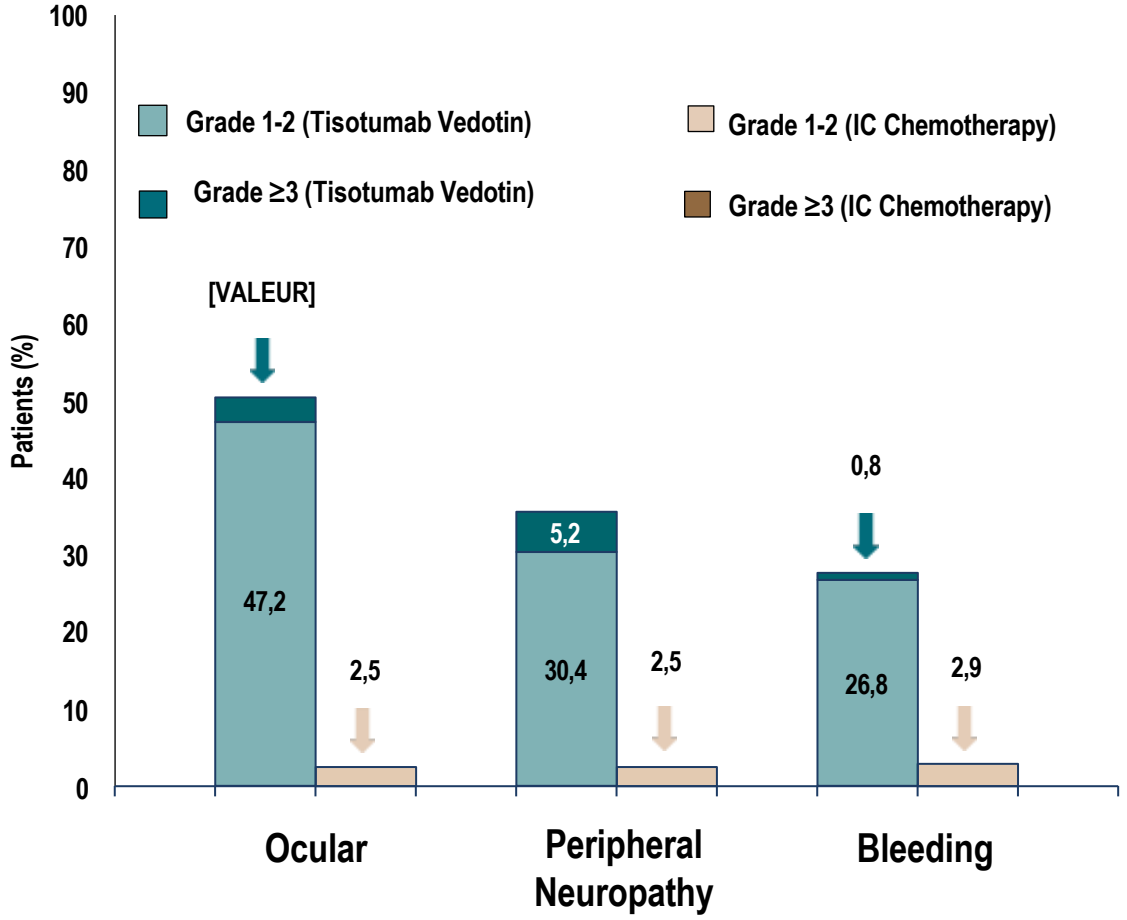
Most Common Treatment-Related Adverse Events[a]



- Grade 5 TRAEs occurred in 2 (0.8%) and 1 (0.4%) patients in the tisotumab vedotin and IC chemotherapy arms, respectively[b]
- Median relative dose intensity was 96.1% and 90.0% in the tisotumab vedotin and IC chemotherapy arms, respectively

[a]TRAEs listed are those occurring in ≥15% of patients on either arm; [b]Grade 5 TRAEs included acute kidney injury (n=1) and Stevens-Johnson syndrome (n=1) in the tisotumab vedotin arm and pancytopenia (n=1) in the IC chemotherapy arm.

Phase 3 innovaTV 301 : A Randomized, Open-Label effets secondaires d'intéret



- There were no grade 4 or 5 AESIs
- Dose discontinuation due to ocular and peripheral neuropathy events occurred in 5.6% of patients for each

Three most common preferred terms for each AESI	
Ocular	Conjunctivitis (30.4%), keratitis (15.6%), dry eye (13.2%)
Peripheral neuropathy	Peripheral sensory neuropathy (26.8%), paresthesia (2.8%), muscular weakness (2.4%), peripheral sensorimotor neuropathy (2.4%)
Bleeding	Epistaxis (22.8%), hematuria (3.2%), vaginal hemorrhage (3.2%)

AESI, adverse event of special interest
[a]Treatment-related AESIs

Phase 3 innovaTV 301 : A Randomized, Open-Label toxicité oculaire

Key Resource and Materials for the Eye Care Plan

Access to eye care professionals

- Complete full eye exam prior to start of treatment administration
- In case of ocular AE: Refer patient to an eye care professional

Eye drops ready for use

1. Vasoconstrictor (Rx):
   e.g. brimonidine tartrate 0.2%
2. Steroid (Rx):
   e.g. dexamethasone 0.1%
3. Lubricating (OTC)

All eye drops are preservative-free

Cooling Pads during infusion

- 2-3 cooling pads per patient per infusion*

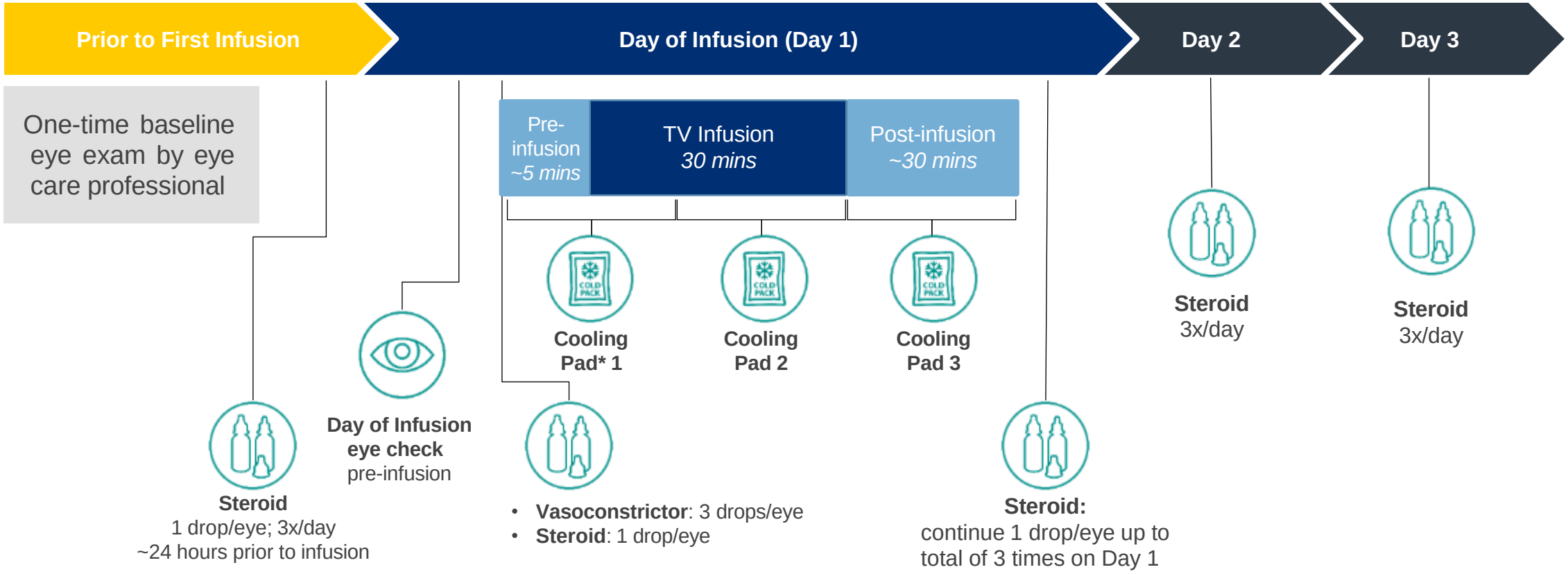
* Based on estimated 30-minute infusion for majority of patients, additional cooling pads may be needed for patients requiring longer infusion time.

Tisotumab vedotin

- Bénéfice Tisotumab vedotin amélioration PFS et OS réduction 30% réduction risque de décès
- Tolérance toxicités particulières saignements, neuropathies, toxicité oculaire précautions particulières, éducation pt , personnel, collaboration avec opthalmologues
- Standard of care de 2e ligne ?

Eye Care Plan

- Risk Mitigation

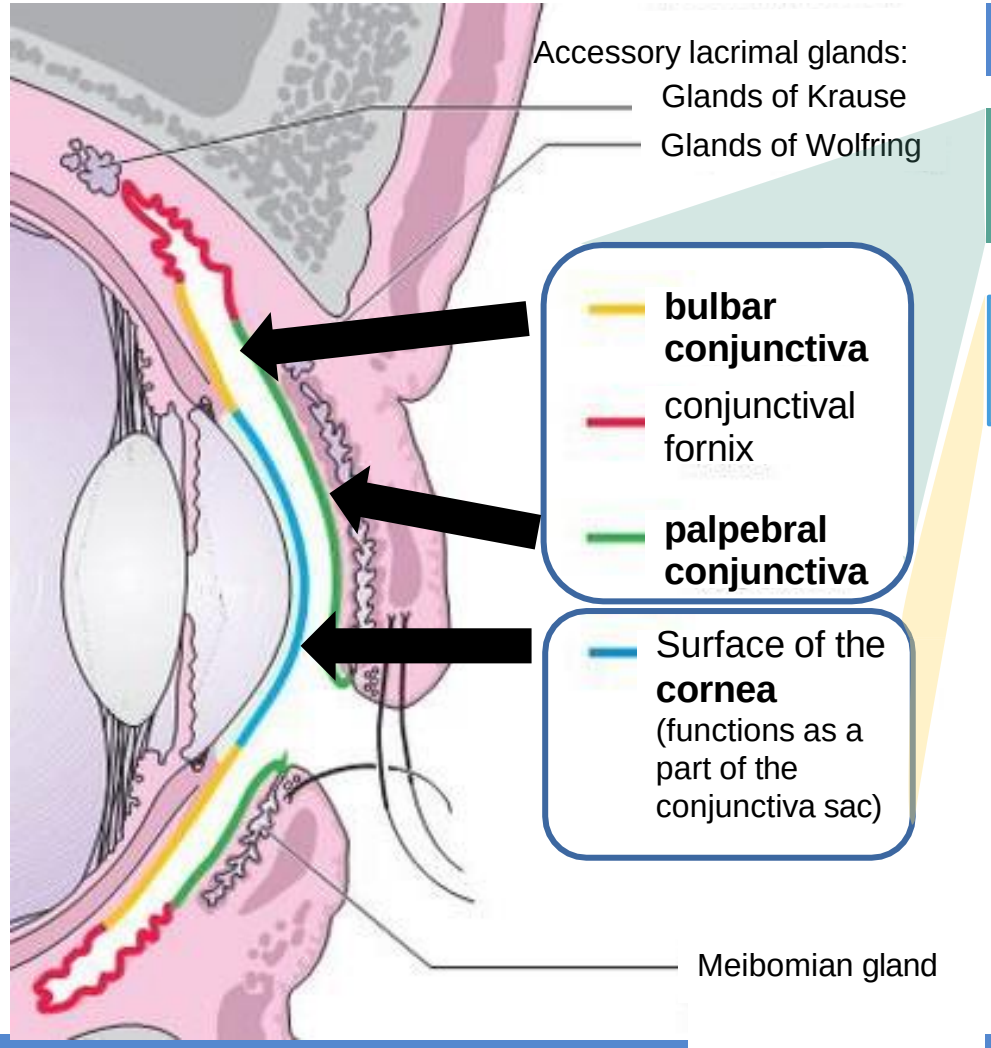


* Each cooling pad is estimated to last ~20 minutes

TV, tisotumab vedotin.

Clinical Data: innovaTV 201 Cervical Cohort

Background on ocular adverse events

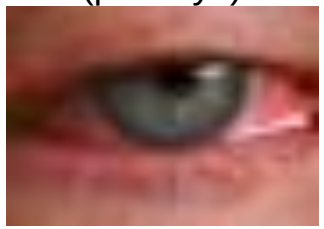


Selected eye anatomy of interest

conjunctiva	Thin layer of tissue that lines the inner surface of the eyelid and covers the white part of the eye
cornea	Outer most layer of the eye that covers the iris and functions in focusing

conjunctivitis

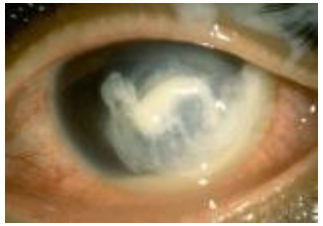
(pink eye)



inflammation of the conjunctiva

keratitis

(corneal ulcer)



inflammation of the cornea

symblepharon

adhesion of the palpebral conjunctiva to the bulbar conjunctiva

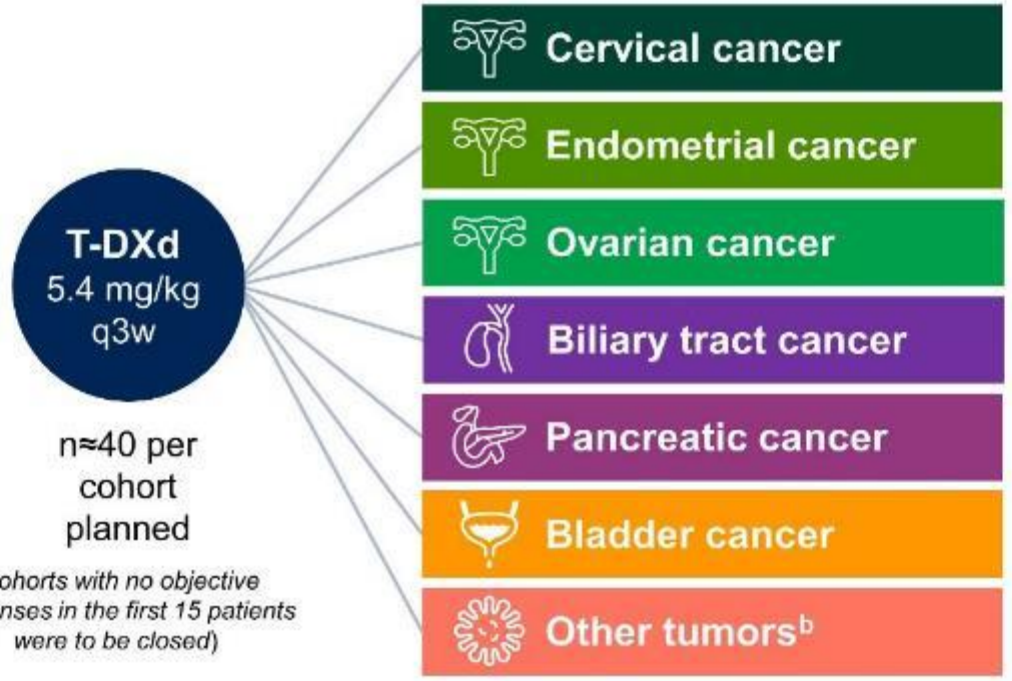
1. AOA.org - conjunctivitis accessed October 8, 2018, 2. NEI.gov - Corneal Disease accessed October 6, 2018, 3. AAO.org - Keratitis , accessed October 6, 2018

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

Trastuzumab deruxtecan

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. [c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

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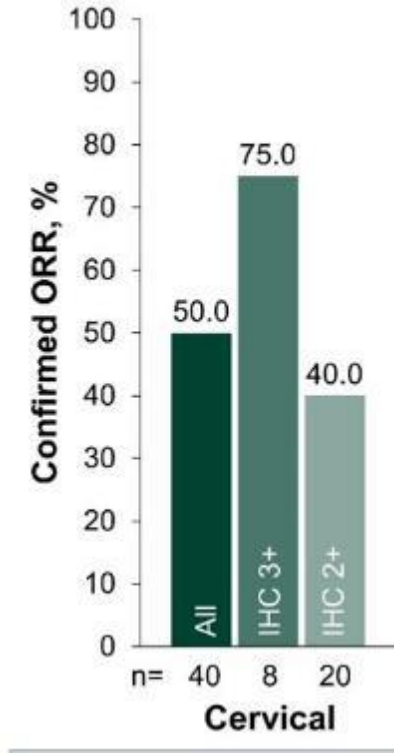
Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)
Investigator assessment				
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)
	PD	7 (17.5)	4 (10.0)	7 (17.5)
	Not evaluable	1 (2.5)	0	1 (2.5)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)



Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

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Conclusion

- Modifications stratégies thérapeutiques dans le K du col métastatique:

  - *immunothérapie* : AMM

✓ en 1ère ligne CPS > 1 en association à la chimiothérapie +/- Beva

✓ en 2e Cemiplimab après chimiothérapie par platine non prétraitée par immunothérapie

  - *ADC*

✓ Tisotumab vedotin bénéfice OS PFS toxicité particulière : en attente accès précoce/AMM

✓ Trastuzumab deruxtecan si tumeur HER2+++ : AMM? Essais avec anti HER2